

PCT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C. 20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|--|--|
| Date of mailing (day/month/year) 28 September 2000 (28.09.00) | Applicant's or agent's file reference 14028.0293/P |
| International application No. PCT/US00/00284 | Priority date (day/month/year) 08 January 1999 (08.01.99) |
| International filing date (day/month/year) 06 January 2000 (06.01.00) | |
| Applicant KNECHTLE, Stuart, J. et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

07 August 2000 (07.08.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Form PCT/IB/331 (July 1992)

Authorized officer

Maria Kirchner

Telephone No.: (41-22) 338.83.38

US0000284

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 11 APR 2001

WIPO

PCT

14

| | | |
|---|---|--|
| Applicant's or agent's file reference 14028.0293/P | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US00/00284 | International filing date (day/month/year) 06/01/2000 | Priority date (day/month/year) 08/01/1999 |
| International Patent Classification (IPC) or national classification and IPC A61K47/48 | | |
| Applicant WISCONSIN ALUMNI RESEARCH FOUNDATION et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 07/08/2000 | Date of completion of this report 09.04.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Bochelen, D Telephone No. +49 89 2399 8150  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/00284

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-36 as originally filed

Claims, No.:

1-33 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/00284

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-33 with respect to industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 1-33 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|------|--------|--------------------|
| Novelty (N) | Yes: | Claims | 1-33 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-33 |
| Industrial applicability (IA) | Yes: | Claims | see separate sheet |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/00284

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/00284

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 1-33** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: KOULMANDA M ET AL: 'Cyclophosphamide, but not CTLA4Ig, prolongs survival of fetal pig islet grafts in anti-T cell monoclonal antibody-treated NOD mice.' XENOTRANSPLANTATION (1998) 5 215-21 , XP000915296
- D2: WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26)
- D3: WO 96 32137 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 17 October 1996 (1996-10-17)
- D4: WO 99 53954 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 28 October 1999 (1999-10-28)
- D5: WO 98 56417 A (THE UNITED STATES OF AMERICA) 17 December 1998 (1998-12-17)
- D6: WO 98 39363 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11)
- D7: WO 95 34320 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 21 December 1995 (1995-12-21)

2. Novelty (Art. 33 (1) and (2) PCT):

The prior art discloses methods to prevent graft rejection by using either inhibitors of T-cell co-stimulation, e.g. CTLA4-Ig (D1: p218 col1 §3; D5: p14 l21; D7: abstract,

claim 7), 5c8 (D2: claim 5), anti-B7 antibody (D7: claim 8), or by reducing the T-cell population with immunotoxins (D3: claims 1, 7; D4: claims 1, 8; D6: claims 1, 27). Document D1 discloses the use of a combination of anti-CD3 or anti-CD4 antibodies and inhibitors of T cell co-stimulation (D1: p218 col2 §2) in order to prevent graft rejection. The subject-matter of **claims 1-28** differs in that a combination of immunotoxins with inhibitors of the co-stimulation are proposed to prevent graft rejection. Therefore, the subject-matter of **claims 1-28 appears to be new**.

The subject-matter of **claims 29-33 is considered to be new**. The prior art discloses the use of immunotoxins to induce immune tolerance by reducing T-cell population and thus to prevent acute graft rejection in the peritransplant period (D3: p18 l7; D4: p9 l10). The subject-matter of **claims 29-23** differs in that the immunotoxins are administered after transplantation when rejection occurs.

3. Inventive step (Art. 33 (1) and (3) PCT):

The subject-matter of **claims 1-28 does not involve an inventive step** for the following reasons.

Document D1, which is considered to be the closest prior art, discloses the combination of anti-CD3 or anti-CD4 antibodies that deplete the T-cell population (D1: abstract, p218 fig3), with an inhibitor of the co-stimulation of T-cells, i.e. CTLA4Ig, in order to prevent graft rejection. The problem underlying the application is therefore to find an alternative method to prevent graft rejection. The solution proposed is to combine co-stimulation blockers with immunotoxins. The prior art discloses the use of immunotoxins, e.g. UCHT1-CRM9 (D4: claim 8) in order to reduce the population of T-cells (D3: claim 1; D4: claim 1) and to prevent graft rejection. Therefore, it would be obvious for a man skilled in the art to use immunotoxins in combination with co-stimulation blockers in order to prevent graft rejection. Moreover, immunotoxins as well as co-stimulation blockers per se are known for their use to prevent graft rejection (see item 2.). The combination of known pharmaceutical compounds in order to obtain the same therapeutical effect as the compounds per se, involves an inventive step only if there is an unexpected advantage over the prior art. The application does not provide any evidence of such an advantage.

Immunotoxins are known for inducing immune tolerance by reducing T-cell

population in the peritransplantation period (D3: p18 l7; D4: p9 l10) The subject-matter of **claims 29-33** differs in that immunotoxin treatment is administered when signs of rejection are detected. It would be obvious for a skilled man to administer the same treatment as used for inducing immune tolerance, in order to reverse the late acute graft rejection by reducing T-cell population. Therefore, the subject-matter of **claims 29-33 does not involve an inventive step.**

4. Industrial applicability (Art (1) and (4) PCT):

For the assessment of the present **claims 1-33** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

5. The units of measure employed on page 17 are not additionally expressed in terms of the units stipulated by Rule 10.1 (a) PCT.
6. The units used on page 20 line 4 and page 24 line 9 are not consistent contrary to the requirement of Rule 10 (2) PCT.

Re Item VIII

Certain observations on the international application

7. The embodiment of the invention described on page 21 does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
8. In **claims 29-33**, the step of monitoring the recipient for signs of rejection is not

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/00284

considered to be a characterizing technical feature since it is a standard procedure following transplantation.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|--|
| Applicant's or agent's file reference 14028.0293/P | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/US 00/ 00284 | International filing date (day/month/year) 06/01/2000 | (Earliest) Priority Date (day/month/year) 08/01/1999 |
| Applicant WISONSIN ALUMNI RESEARCH FOUNDATION et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PC 00/00284

| A. CLASSIFICATION OF SUBJECT MATTER | | |
|---|--|--|
| IPC 7 A61K47/48 A61K39/395 A61K38/17 A61K38/13 A61K31/4353 A61K31/52 A61K31/56 //(A61K47/48,39:395),(A61K47/48,38:17), (A61K47/48,38:13),(A61K47/48,31:4353),(A61K47/48,31:52), According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED | | |
| Minimum documentation searched (classification system followed by classification symbols) | | |
| IPC 7 A61K | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used) | | |
| EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | KOULMANDA M ET AL: "Cyclophosphamide, but not CTLA4Ig, prolongs survival of fetal pig islet grafts in anti-T cell monoclonal antibody-treated NOD mice." XENOTRANSPLANTATION (1998) 5 215-21 , XP000915296 abstract | 1-6, 11-13 |
| Y | WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26) claims 1-28 | 1-33 |
| Y | WO 96 32137 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 17 October 1996 (1996-10-17) claims 1-38 | 1-33 |
| -/-- | | |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. | | |
| * Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family | | |
| Date of the actual completion of the international search | | Date of mailing of the international search report |
| 10 July 2000 | | 25/07/2000 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | | Authorized officer Le Flao, K |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/00284

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (A61K47/48,31:56)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 99 53954 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 28 October 1999 (1999-10-28) claim 8 | 10 |
| A | WO 98 56417 A (THE UNITED STATES OF AMERICA) 17 December 1998 (1998-12-17) claims 1-16 | 1-33 |
| A | WO 98 39363 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11) claims 1-42 | 1-33 |
| A | WO 95 34320 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 21 December 1995 (1995-12-21) claims 1-77 | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 July 2000

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Le Flao, K

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/00284

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|---|--|
| WO 9852606 | A | 26-11-1998 | AU 7494098 A EP 0980259 A NO 995617 A AU 7956798 A EP 1009432 A WO 9856417 A | 11-12-1998 23-02-2000 17-01-2000 30-12-1998 21-06-2000 17-12-1998 |
| WO 9632137 | A | 17-10-1996 | AU 5663796 A CA 2218166 A EP 0830146 A US 5762927 A | 30-10-1996 17-10-1996 25-03-1998 09-06-1998 |
| WO 9953954 | A | 28-10-1999 | AU 3654499 A | 08-11-1999 |
| WO 9856417 | A | 17-12-1998 | AU 7494098 A AU 7956798 A EP 0980259 A EP 1009432 A NO 995617 A WO 9852606 A | 11-12-1998 30-12-1998 23-02-2000 21-06-2000 17-01-2000 26-11-1998 |
| WO 9839363 | A | 11-09-1998 | AU 6542698 A EP 1015496 A | 22-09-1998 05-07-2000 |
| WO 9534320 | A | 21-12-1995 | AU 2701895 A CA 2191733 A EP 0784482 A JP 10501815 T | 05-01-1996 21-12-1995 23-07-1997 17-02-1998 |

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

To:

NEEDLE & ROSENBERG, P.C.
Suite 1200
Attn. SPRATT, G.
The Candler Building
127 Peachtree Street, N.E.
Atlanta, GA 30303-1811
UNITED STATES OF AMERICA

RECEIVED

JUL 1 2000

NEEDLE & ROSENBERG

(PCT Rule 44.1)

Date of mailing
(day/month/year)

25/07/2000

Applicant's or agent's file reference

14028.0293/P

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 00/00284

International filing date
(day/month/year)

06/01/2000

Applicant

WISONSIN ALUMNI RESEARCH FOUNDATION et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

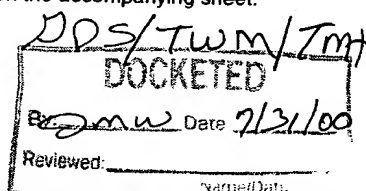
Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.



2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Catherine Humbert

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|--|--|
| Applicant's or agent's file reference 14028.0293/P | FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small> | |
| International application No. PCT/US 00/ 00284 | International filing date (day/month/year) 06/01/2000 | (Earliest) Priority Date (day/month/year) 08/01/1999 |
| Applicant WISONSIN ALUMNI RESEARCH FOUNDATION et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

CT/US 00/00284

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 A61K39/395 A61K38/17 A61K38/13 A61K31/4353
A61K31/52 A61K31/56 //(A61K47/48,39:395),(A61K47/48,38:17),
(A61K47/48,38:13),(A61K47/48,31:4353),(A61K47/48,31:52),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | KOULMANDA M ET AL: "Cyclophosphamide, but not CTLA4Ig, prolongs survival of fetal pig islet grafts in anti-T cell monoclonal antibody-treated NOD mice." XENOTRANSPLANTATION (1998) 5 215-21 , XP000915296 abstract | 1-6, 11-13 |
| Y | WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26) claims 1-28 | 1-33 |
| Y | WO 96 32137 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 17 October 1996 (1996-10-17) claims 1-38 | 1-33 |
| | --- -/-- | |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 July 2000

Date of mailing of the international search report

25/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Le Flao, K

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (A61K47/48,31:56)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 99 53954 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 28 October 1999 (1999-10-28) claim 8 | 10 |
| A | WO 98 56417 A (THE UNITED STATES OF AMERICA) 17 December 1998 (1998-12-17) claims 1-16 | 1-33 |
| A | WO 98 39363 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11) claims 1-42 | 1-33 |
| A | WO 95 34320 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 21 December 1995 (1995-12-21) claims 1-77 | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 July 2000

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Le Flao, K



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/00284

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

R mark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/00284

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|---|--|
| WO 9852606 | A | 26-11-1998 | AU 7494098 A EP 0980259 A NO 995617 A AU 7956798 A EP 1009432 A WO 9856417 A | 11-12-1998 23-02-2000 17-01-2000 30-12-1998 21-06-2000 17-12-1998 |
| WO 9632137 | A | 17-10-1996 | AU 5663796 A CA 2218166 A EP 0830146 A US 5762927 A | 30-10-1996 17-10-1996 25-03-1998 09-06-1998 |
| WO 9953954 | A | 28-10-1999 | AU 3654499 A | 08-11-1999 |
| WO 9856417 | A | 17-12-1998 | AU 7494098 A AU 7956798 A EP 0980259 A EP 1009432 A NO 995617 A WO 9852606 A | 11-12-1998 30-12-1998 23-02-2000 21-06-2000 17-01-2000 26-11-1998 |
| WO 9839363 | A | 11-09-1998 | AU 6542698 A EP 1015496 A | 22-09-1998 05-07-2000 |
| WO 9534320 | A | 21-12-1995 | AU 2701895 A CA 2191733 A EP 0784482 A JP 10501815 T | 05-01-1996 21-12-1995 23-07-1997 17-02-1998 |

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APR 16 2001

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

NEEDLE & ROSENBERG

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

To:

McKEON, Tina W.
NEEDLE & ROSENBERG, P.C.
Suite 1200
The Candler Building
127 Peachtree Street, N.E.
Atlanta, GA 30303
ETATS-UNIS D'AMERIQUE

Date of mailing
(day/month/year) 09.04.2001

Applicant's or agent's file reference
14028.0293/P

IMPORTANT NOTIFICATION

International application No.
PCT/US00/00284

International filing date (day/month/year)
06/01/2000

Priority date (day/month/year)
08/01/1999

Applicant
WISCONSIN ALUMNI RESEARCH FOUNDATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

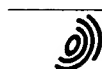
The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

205/Twm/Tmh
DOCKETED
By Twm Date 4/16/01
Reviewed Twm 4/16/01
Name / Date

Name and mailing address of the IPEA/



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D-80298 Munich
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Authorized officer

Hundt, D

Tel. +49 89 2399-8042



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|--|
| Applicant's or agent's file reference 14028.0293/P | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US00/00284 | International filing date (day/month/year) 06/01/2000 | Priority date (day/month/year) 08/01/1999 |
| International Patent Classification (IPC) or national classification and IPC A61K47/48 | | |
| Applicant WISCONSIN ALUMNI RESEARCH FOUNDATION et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 07/08/2000 | Date of completion of this report 09.04.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Bochelen, D Telephone No. +49 89 2399 8150  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/00284

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-36 as originally filed

Claims, No.:

1-33 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/00284

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-33 with respect to industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 1-33 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
 - ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|------|--------|--------------------|
| Novelty (N) | Yes: | Claims | 1-33 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-33 |
| Industrial applicability (IA) | Yes: | Claims | see separate sheet |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/00284

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/00284

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 1-33** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: KOULMANDA M ET AL: 'Cyclophosphamide, but not CTLA4Ig, prolongs survival of fetal pig islet grafts in anti-T cell monoclonal antibody-treated NOD mice.' XENOTRANSPLANTATION (1998) 5 215-21 , XP000915296
- D2: WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26)
- D3: WO 96 32137 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 17 October 1996 (1996-10-17)
- D4: WO 99 53954 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 28 October 1999 (1999-10-28)
- D5: WO 98 56417 A (THE UNITED STATES OF AMERICA) 17 December 1998 (1998-12-17)
- D6: WO 98 39363 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11)
- D7: WO 95 34320 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 21 December 1995 (1995-12-21)

2. Novelty (Art. 33 (1) and (2) PCT):

The prior art discloses methods to prevent graft rejection by using either inhibitors of T-cell co-stimulation, e.g. CTLA4-Ig (D1: p218 col1 §3; D5: p14 l21; D7: abstract,

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/00284

claim 7), 5c8 (D2: claim 5), anti-B7 antibody (D7: claim 8), or by reducing the T-cell population with immunotoxins (D3: claims 1, 7; D4: claims 1, 8; D6: claims 1, 27). Document D1 discloses the use of a combination of anti-CD3 or anti-CD4 antibodies and inhibitors of T cell co-stimulation (D1: p218 col2 §2) in order to prevent graft rejection. The subject-matter of **claims 1-28** differs in that a combination of immunotoxins with inhibitors of the co-stimulation are proposed to prevent graft rejection. Therefore, the subject-matter of **claims 1-28 appears to be new.**

The subject-matter of **claims 29-33 is considered to be new.** The prior art discloses the use of immunotoxins to induce immune tolerance by reducing T-cell population and thus to prevent acute graft rejection in the peritransplant period (D3: p18 l7; D4: p9 l10). The subject-matter of **claims 29-23** differs in that the immunotoxins are administered after transplantation when rejection occurs.

3. Inventive step (Art. 33 (1) and (3) PCT):

The subject-matter of **claims 1-28 does not involve an inventive step** for the following reasons.

Document D1, which is considered to be the closest prior art, discloses the combination of anti-CD3 or anti-CD4 antibodies that deplete the T-cell population (D1: abstract, p218 fig3), with an inhibitor of the co-stimulation of T-cells, i.e. CTLA4Ig, in order to prevent graft rejection. The problem underlying the application is therefore to find an alternative method to prevent graft rejection. The solution proposed is to combine co-stimulation blockers with immunotoxins. The prior art discloses the use of immunotoxins, e.g. UCHT1-CRM9 (D4: claim 8) in order to reduce the population of T-cells (D3: claim 1; D4: claim 1) and to prevent graft rejection. Therefore, it would be obvious for a man skilled in the art to use immunotoxins in combination with co-stimulation blockers in order to prevent graft rejection. Moreover, immunotoxins as well as co-stimulation blockers per se are known for their use to prevent graft rejection (see item 2.). The combination of known pharmaceutical compounds in order to obtain the same therapeutical effect as the compounds per se, involves an inventive step only if there is an unexpected advantage over the prior art. The application does not provide any evidence of such an advantage.

Immunotoxins are known for inducing immune tolerance by reducing T-cell

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/00284

population in the peritransplantation period (D3: p18 l7; D4: p9 l10) The subject-matter of **claims 29-33** differs in that immunotoxin treatment is administered when signs of rejection are detected. It would be obvious for a skilled man to administer the same treatment as used for inducing immune tolerance, in order to reverse the late acute graft rejection by reducing T-cell population. Therefore, the subject-matter of **claims 29-33 does not involve an inventive step.**

4. Industrial applicability (Art (1) and (4) PCT):

For the assessment of the present **claims 1-33** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

5. The units of measure employed on page 17 are not additionally expressed in terms of the units stipulated by Rule 10.1 (a) PCT.
6. The units used on page 20 line 4 and page 24 line 9 are not consistent contrary to the requirement of Rule 10 (2) PCT.

Re Item VIII

Certain observations on the international application

7. The embodiment of the invention described on page 21 does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
8. In **claims 29-33**, the step of monitoring the recipient for signs of rejection is not

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/00284

considered to be a characterizing technical feature since it is a standard procedure following transplantation.

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